

Attorney Docket No.: KUZ0031US.NP
Inventors: Minoru Kohara
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Amendments to the specification:

Please replace the paragraph beginning at page 1 and following [0002] with the following paragraph:

Although conventionally, the therapy of a disease was generally made by an oral administration or parenteral administration of a drug was general, relatively recently a method to transdermally administer a drug into the body has been used. As a characteristic of a transdermal absorption preparation, it adheres closely for 24 to 48 hours in general, whereby absorption of a designated amount of a drug is necessary, and it is necessary that it adheres closely and does not peel off even when sweating or having a bath. In addition, it is also necessary that it can be peeled off with a peeling force in such a degree as not to be painful when peeling off, and if a pressure-sensitive adhesiveness is strong beyond necessity, hair ~~tearing~~ plucking or keratin ~~ablation~~ peeling occur when peeling off, while a mechanistic skin irritation due to pulling of the skin is produced. As the results, ~~rash~~ erythema occurs and in a severe case incrustation or edema formation are accompanied, whereby these last for several days after peeling off; and therefore, it is necessary to minimize these inconveniences as much as possible. In addition, it is also necessary not

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to let a pressure-sensitive adhesive agent remain on a skin surface after peeling off a transdermal absorption preparation from the skin.

Please replace the paragraph beginning at page 5 and following [0009] with the following paragraph:

In addition, the invention relates to the above pressure-sensitive adhesive composition, wherein the alkyl (meth)acrylate is one or more consisting of an alcohol ester with an alkyl group of carbon numbers ~~4-6~~ 4-12, a content thereof being from 30 to 80% by weight based on the entire copolymer, a content of hydroxyethyl (meth)acrylate is from 3 to 25% by weight based on the entire copolymer, and a content of N-vinyl-2-pyrrolidone is from 5 to 25% by weight based on the entire copolymer.

Please replace the paragraph beginning at page 6 and following [0014] with the following paragraph:

By making an acrylic copolymer (containing from 3 to 25% by weight of hydroxyethyl ~~(meth)acryrate~~ (meth)acrylate in copolymers), a plasticizer and a pseudo-crosslinking compound as essential components, and by making the ratio of the content of the plasticizer to the content of the pseudo-crosslinking compound from 30:1 to 250:1, the invention attains an appropriate balance of a pressure-sensitive

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adhesive property, a cohesive property and a skin irritation, and also attains a skin sticking property, that is, a follow-up property at a sticking part.

Please replace the paragraph beginning at page 7 and following [0016] with the following paragraph:

In addition, in the invention, a composition, in which a cohesive force is particularly excellent and the problem of a glue residue is further favorably solved, can be provided by one in which alkyl (meth)acrylate is one or more consisting of an alcohol ester with an alkyl group of carbon numbers ~~4-6~~ 4-12, a content thereof being from 30 to 80% by weight based on the entire copolymer, a content of hydroxyethyl (meth)acrylate is from 3 to 25% by weight based on the entire copolymer, and a content of N-vinyl-2-pyrrolidone is from 5 to 25% by weight based on the entire copolymer.

Please replace the paragraph beginning at line 9 of page 8 with the following paragraph:

In the invention, a ~~composition~~ composition, in which the problem of a glue residue is further favorably solved, can be provided by one in which the pseudo-crosslinking compound is one or more from boric acid and/or salts

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thereof, an amine compound, an aluminate and a phenol compound.

Please replace the paragraph beginning at line 14 of page 9 with the following paragraph:

In order to give a higher pressure-sensitive adhesive property, the acrylic copolymer in the composition of the invention contains alkyl (meth)acrylate, which consists of an ester with an alcohol of carbon numbers ~~4-6~~ 4-12 of an alkyl group, from 30 to 80% by weight, preferably from 40 to 70% by weight. Examples include butyl (meth)acrylate, isobutyl (meth)acrylate, hexyl acrylate, octyl acrylate, 2-ethylhexyl (meth)acrylate, isooctyl (meth)acrylate, dodecyl (meth)acrylate, and the like, while these may be used singly or in a combination. By making the content of alkyl (meth)acrylate not less than 30%, a higher pressure-sensitive adhesive property is attained, and by making it not more than 80%, a high cohesive force improvement by a pseudo-crosslinking which is a main aim of the invention is attained.

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Please replace the paragraph beginning at page 11 and following [0025] with the following paragraph:

As the above-described ~~Azores~~ Azobis type polymerization initiator, illustrative are, for example, 2,2'-azobisisobutyronitrile, 1,1'-azobis(cyclohexane-1-carbonitrile), 2,2'-azobis-(2,4-dimethylvaleronitrile), and the like, and as the above-described peroxide type polymerization initiator, illustrative are, for example, lauroyl peroxide, benzoyl peroxide, di-*tert*-butyl peroxide, and the like.

Please replace the paragraph beginning at page 12 and following [0026] with the following paragraph:

In order to prepare the composition of the invention, a plasticizer is added to the above-described acrylic copolymer. The added amount of said plasticizer is preferably from 30 to 200 parts relative to 100 parts by ~~weigh~~ weight of the acrylic copolymer. By making the added amount not less than 30 parts, a patch less in a skin irritation property can be obtained, and by making it not more than 200 parts, a higher cohesive force in a pressure-sensitive adhesive agent type by a pseudo-crosslinking described below can be obtained.

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Please replace the paragraph beginning at line 1 of page 14 with the following paragraph:

As the amine ~~amine~~ compound, illustrative are monoamine compounds such as propylamine, diamine compounds such as hexanediamine and ethylenediamine, and triamine compounds such as diethylenetriamine. The diamine compounds are preferable, and hexanediamine and ethylenediamine are particularly preferable.

Please replace the paragraph beginning at page 17 and following [0036] with the following paragraph:

Although the patch of the invention constitutes lamination of the above-described acrylic composition layer on one side of a backing, further it can be made a ~~transdermal~~ transdermal absorption preparation or a patch type cosmetic preparation by addition of a skin valuable.

Please replace the paragraph beginning at page 17 and following [0037] with the following paragraph:

The above-described backing is preferably one which is non-permeable or scarcely permeable for a drug and soft, illustrative are, for example, resin films such as polyethylene, polypropylene, ethylene-methyl acrylate copolymer, ethylene-vinyl acetate copolymer, polyvinylidene chloride, polyurethane, nylon, polyethylene terephthalate,

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~~polybutylene~~ polybutylene terephthalate, and the like; aluminum sheet and the like, and may be a laminated sheet of these or may be laminated with a woven fabric or a non-woven fabric. In addition, to increase a sticking property with the pressure-sensitive adhesive layer, a surface treatment such as corona treatment, plasma discharge treatment, or the like may be operated, or anchor coating treatment by an anchor agent may be operated.

Please replace the paragraph beginning at page 18 and following [0038] with the following paragraph:

The drug as a skin valuable contained in the above-described composition is not particularly limited as long as it can ~~transdermally~~ transdermally permeate a biomembrane; illustrative are, for example, antipyretic-analgesic agents, steroidal anti-inflammatory agents, vasodilators, antiarrhythmic agents, hypotensors, local anesthetics, hormonal agents, anti-histaminic agents, general anesthetics, hypnotic-sedatives, anti-epileptic agents, ~~psycho—neuro~~ psychoneurotic agents, skeletal muscle relaxants, agents for the autonomic nervous system, anti Parkinsonism agents, diuretics, vasoconstrictors, respiratory stimulants, narcotics, and the like.

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Please replace the paragraph beginning at line 1 of page 19 with the following paragraph:

As the above-described vasodilators, illustrative are, for example, diltiazem hydrochloride, pentaerythritol tetranitrate, isosorbide nitrate, and the like. As the above-described antiarrhythmic agents, illustrative are, for example, procainamide hydrochloride, disopyramide, mexiletine hydrochloride, and the like. As the above-described hypotensors, illustrative are, for example, clonidine hydrochloride, ~~bunitrol~~ bunitrolol hydrochloride, captopril, and the like. As the above-described local anesthetics, illustrative are, for example, ethyl aminobenzoate, tetracaine hydrochloride, procaine hydrochloride, dibucaine hydrochloride, oxybuprocaine hydrochloride, propitocaine hydrochloride, and the like. As the above-described hormonal agents, illustrative are, for example, propylthiouracil, thiamazole, metenolone acetate, estradiol, estriol, progesterone, and the like. As the above-described antihistamines, illustrative are, for example, diphenhydramine hydrochloride, chlorpheniramine maleate, promethazine, cyproheptadine hydrochloride, diphenylpyraline hydrochloride, and the like.

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Please replace the paragraph beginning at line 1 of page 20 with the following paragraph:

As the above-described ~~psycho—neuro~~ psychoneurotic agents, illustrative are, for example, chlorpromazine hydrochloride, thioridazine, meprobamate, imipramine hydrochloride, chlordiazepoxide, diazepam, and the like. As the above-described skeletal muscle relaxants, illustrative are, for example, suxamethonium hydrochloride, eperisone hydrochloride, and the like. As the above-described agents for the autonomic nervous system, illustrative are, for example, neostigmine bromide, bethanechol chloride, and the like. As the above-described anti Parkinsonism agents, illustrative are, for example, amantadine hydrochloride, and the like. As the above-described diuretics, illustrative are, for example, hydroflumethiazide, isosorbide, furosemide, and the like.

Please replace the paragraph beginning at page 20 and following [0043] with the following paragraph:

As the above-described vasoconstrictors, illustrative are, for example, phenylephrine hydrochloride, and the like. As the above-described respiratory stimulants, illustrative are, for example, lobeline hydrochloride, dimorpholamine, ~~naloxaone~~ naloxone hydrochloride, and the like. As the

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above-described narcotics, illustrative are, for example, morphine hydrochloride, codeine phosphate, cocaine hydrochloride, pethidine hydrochloride, and the like.

Please replace the paragraph beginning at page 22 and following [0047] with the following paragraph:

For preparation of a transdermal absorption preparation of the invention, a preparation method of a conventionally known pressure-sensitive adhesive tape (patch) can be used. For example, in a solvent coating method, the pressure-sensitive adhesive agent, the plasticizer, the pseudo-crosslinking compound and the skin valuable of a designated amount are dissolved or dispersed in solvent such as ethyl acetate, and a method to ~~apply~~ coat and dry an obtained liquid on a backing, a method to ~~apply~~ coat and dry it on a release paper and then to transfer it on a backing, and the like are preferably used.

Please replace Table 1 beginning at page 25 with the following:

Table 1

Example	Acrylic copolymer solid part (weight ratio)	Plasticizer (weight ratio)	Pseudo-crosslinking compound (weight ratio)	Shearing strain migration length (mm)	
				(3g, 2min.)	(80g, 5min.)

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4	Example 1(100)	IPM (50)	Boric acid (1.0)	0	<input type="checkbox"/> 2
5	Example 1(100)	IPP (60)	Boric acid (15) <u>(1.5)</u>	0	<input type="checkbox"/> 2
7	Example 2(100)	Diethyl sebacate (60)	Ammonium borate octahydrate(1.8)	0	<input type="checkbox"/> 2

Please replace the paragraph beginning at line 21 of page 28 with the following paragraph:

0: No ~~rash~~ erythema, 1: Very slight ~~rash~~ erythema in a barely detectable degree, 2: Apparent ~~rash~~ erythema, 3: ~~Rash~~ erythema in a medium degree, 4: Strong ~~rash~~ erythema with a deep red color

Please replace the paragraph beginning at line 12 of page 30 with the following paragraph:

A test piece (2.5x2.5cm) of the tape preparation was stuck on a shaven back of a Japanese White rabbit and peeled off after 24 hours. A skin ~~rash~~ erythema condition after 1 hour from peeling off was observed by visual inspection. Further, in the test, the formation of edema and incrustation was not detected. Each preparation was stuck to 4 rabbits in total. The degree of ~~rash~~ erythema was evaluated according to the below evaluation standard by 5

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steps of 0-4. 0: no ~~rash~~ erythema, 1: very slight ~~rash~~ erythema in a barely detectable degree, 2: apparent ~~rash~~ erythema, 3: ~~rash~~ erythema in a medium degree, 4: strong ~~rash~~ erythema with a deep red color. The mean value of the total sum of an evaluation point in each rabbit, which was divided by 4, was made a skin irritation index number of each tape preparation.

Please replace the paragraph beginning at page 33 and following [0072] with the following paragraph:

In Table 7 described below, the compositions and the measurement results of shearing strain migration length of the pressure-sensitive adhesive sheets for the skin (patches), which were prepared and measured above, are shown as the examples. In Table 8, as the comparative examples, the results prepared and measured according to the examples are shown. Further, as to the pseudo-crosslinking compounds, each of a reagent special grade was used. In practical blending, oxo acid was added in a designated amount as 5% aqueous solution. A case in which the shearing strain migration length is more than 2mm was made □2. Other pseudo-crosslinking compounds were added in a designated amount as 5% ~~tetrahydrofuran~~ tetrahydrofuran solution.

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Please replace Table 7 at page 34 with the following:

Table 7

Example	Acrylic copolymer solid part (weight ratio)	Plasticizer (weight ratio)	Pseudo- crosslinking compound (weight ratio)	Shearing strain migration length (mm)	
				(3g, 2min.)	(80g, 5min.)
20	Example 18 (100)	IPP (50) (60)	Sodium aluminate (0.5)	0	□2
21	Example 18 (100)	Myrystyl lactate (70)	Resorcinol (0.7)	0	□2
22	Example 19 (100)	IPP (80)	Ammonium borate octahydrate (2.0)	0	□2

Please replace the paragraph beginning at page 35 and following [0075] with the following paragraph:

Since the composition and the patch (~~transdermal~~
transdermal absorption preparation, cosmetic sheet) using it
 is the constitution as described above, a favorable sticking
 property with well-balanced pressure-sensitive adhesiveness
 and cohesive force is shown; and therefore, when peeling off
 there is no glue residue, and a skin irritation due to a
 mechanical irritation and the like such as injury of a
 keratin layer of a skin surface and hair ~~tearing~~ plucking
 can be reduced. Consequently, the invention greatly

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contributes to the development of patch production
industries and the related industries.